



Twenty-year Experience of Post-transplant Lymphoproliferative Disorders in Liver Transplantation, Assessment of Risk Factors, Disease Management and Survival

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Abstract

Background: Post-transplant Lymphoproliferative Disorder (PTLD) is a rare complication that occurs post transplantation. Prognosis and mortality are not well established in adult Liver Transplant (LT). In this study we review LT patients who develop PTLD.

Methods: We retrospectively reviewed adult LT PTLD over a twenty-year period at our transplant center. Diagnosis was confirmed by biopsy. Patient characteristics and survival were assessed.

Results: Nineteen patients had PTLD. Majority were Caucasian, age of 50 years with a slight male predominance at LT. Most common indication for LT was primary sclerosing cholangitis. Median time from LT to diagnosis was 6.48 years. Diffuse large B cell lymphoma was the most common form of PTLD, with a minority of only three patients having EBV in tumor pathology. Five patients passed away within a median of 3.7 months from PTLD diagnosis. Overall 5-year survival from PTLD diagnosis was 77.6%.

Conclusion: Low incidence of PTLD in LT with heterogeneous presentations makes early diagnosis difficult. Use of EBV monitoring to aide detection may be insufficient as the sole screening method. A higher suspicion for vague symptoms may be used in patients with PSC disease. These findings highlight need for multicenter collaborations to better understand this condition.

Abbreviations

AIH: Auto Immune Hepatitis; CMV: Cyto Megalo Virus; DLBCL: Diffuse Large B Cell Lymphoma; EBV: Epstein Barr Virus; ESLD: End Stage liver Disease; HBV: Hepatitis B Virus; HCC: Hepato Cellular Carcinoma; HCV: Hepatitis C Virus; ISR: Immuno Suppression Reduction; LT: Liver Transplant; LN: Lymph Node; MTX: Methotrexate; MMF: Mycophenolate Mofetil; NASH: Non-Alcoholic Steato Hepatitis; PSC: Primary Sclerosing Cholangitis; PTLD: Post-Transplant Lymphoproliferative Disorder; R-CHOP: (Rituximab, Cyclophosphamide, Doxorubicin, Oncovin, Prednisone); XRT: Radiation Therapy

Introduction

Post-Transplant Lymphoproliferative Disorders (PTLD) are lymphoid proliferations occurring in the setting of immunosuppression in transplant recipients. The World Health Organization categorizes PTLD into 6 categories ranging from benign hyperplasia to dysplasia [1]. Of these categories: Diffuse large B cell lymphoma with CD20 positivity comprises the bulk of reported PTLD [2]. Though uncommon: PTLD can account for approximately 20% of cancers following organ transplantation [3,4]. Most cases (>50 percent) are diagnosed within the first-year post-transplant with reported incidence of one percent at 10 years. Compared to lymphoma in the general population: this represents a higher relative risk of 11.8-fold [5-7].

Epstein-Barr virus (EBV) viremia is thought to have a significant role in the development of PTLD [8]. The risk is high in donor to recipient mismatch of EBV status and EBV sero negative patients where seroconversion can occur [9]. Immunosuppression regimens play a key role in organ survival following transplantation. Their potency however comes at a price as immunosuppressive

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Table 1: Patient Characteristics at time of transplant and biopsy proven rejection.

Sno	LT Indication	Age	Gender	Race	CMV IgG†	Post LT immunosuppression	ACR‡
1	HCV/ alcohol	50	Male	Caucasian	Seronegative	Tacrolimus 1 mg BID	1
2	AIH/A1AT	56	Female	Caucasian	Seropositive	Tacrolimus 4 mg BID, MMF 1 g BID	0
3	PSC	58	Male	Caucasian	Seropositive	Tacrolimus 1 mg BID, MMF 1.5 g BID	0
4	HCV	55	Male	Caucasian	Seronegative	Tacrolimus 5 mg BID, MMF 1 g BID	1
5	AIH	40	Female	Caucasian	Seropositive	Tacrolimus 2.5 mg BID, MMF 750 mg BID	2
6	NASH	66	Male	Caucasian	Seronegative	Tacrolimus 2 mg BID, MMF 500 mg BID	0
7	PSC	37	Male	Caucasian	Seronegative	Tacrolimus 5 mg BID	1
8	PSC	45	Female	Caucasian	Seropositive	Tacrolimus 2.5 mg BID, MMF 750 mg BID	0
9	PSC	47	Male	Caucasian	Seronegative	Tacrolimus 2.5 mg BID, MMF 1 g BID	0
10	PSC/HCC	19	Female	Caucasian	Seropositive	Tacrolimus 1 mg BID, MMF 750 mg BID	2
11	HCV	43	Female	Hispanic	Seropositive	Tacrolimus 4 mg BID, MMF 1 g BID	2
12	PSC	41	Male	Caucasian	Seropositive	Tacrolimus 1.5 mg, MMF 1 g BID	1
13	Hemochromatosis	57	Male	Caucasian	Seropositive	Tacrolimus 4 mg BID, MMF 1 g BID	0
14	PSC	42	Female	Hispanic	Seropositive	Tacrolimus 3 mg BID, MMF 1 g BID	0
15	HCV/HCC	55	Male	Caucasian	Seropositive	Tacrolimus 1 mg BID, MMF 500 mg BID	1
16	HBV	58	Male	Asian	Seropositive	Imuran followed by Tacrolimus 1mgBID, MMF 500 mg BID	2
17	PSC	56	Female	Caucasian	Seropositive	Tacrolimus 2.5 mg BID	1
18	Hemochromatosis	57	Female	Caucasian	Seropositive	Tacrolimus 4 mg BID	0
19	PBC	23	Female	Caucasian	Seropositive	Tacrolimus 2 mg BID, MMF 500 mg BID	1

†All patients were EBV (Epstein Barr Virus) seropositive at transplant

‡ ACR is the number of biopsy proven rejection episodes between date of transplant and PTLD diagnosis

ACR: Acute Cellular Rejection; AIH: Auto Immune Hepatitis; A1AT: Alpha 1 Antitrypsin Deficiency; BID: Twice Daily; CMV: Cyto Megalo Virus; HCC: Hepato Cellular Carcinoma; HCV: Hepatitis C Virus; LT: Liver Transplant; MMF: Mycophenolate Mofetil (CellCept); NASH: Non-Alcoholic Steato Hepatitis; PSC: Primary Sclerosing Cholangitis

agents such as calcineurin inhibitors and anti-lymphocyte therapy: can mediate clonal expansion of EBV affect B cells by drug effect on T cell suppression [10]. Younger age: specifically pediatric group: has been associated with higher incidence of PTLD: likely due to the higher number of EBV seronegative transplant patients [11]. On the other hand: age >50 has also been noted to have a higher correlation with PTLD development [12].

As lung and interstitial organs have abundance of lymphoid tissue: PTLD is most commonly noted in these organs [13]. In Liver Transplant (LT): reported PTLD ranges from 1% to 2% in the adult population with cumulative incidence over five years noted to be from 1% to 2% [14,15]. Factors such as EBV status: age and type of immunosuppression in LT are studied and extrapolated based on PTLD presentation in other solid organ transplants. However: risk factors for PTLD in adult LT recipients are not well established given low incidence and limited literature. In this study: we review the clinical characteristics and mortality of adult LT recipients who developed PTLD at a single LT center.

Materials and Methods

This retrospective study was conducted at the transplant center in University of Florida: Gainesville: Florida. Institutional review board approval was obtained prior to commencing the review. The LT database was searched over the period 1997-2018. Using ICD-9 and ICD-10 codes for PTLD: charts were identified to review. Patients who were ≥ 18 years old at the time of transplant and had biopsy proven histopathological diagnosis of PTLD were included. Their charts were evaluated for baseline characteristics at time of transplant including EBV and Cyto Megalo Virus (CMV) serostatus. The type and dosage

of immunosuppressive agents post-transplant were collected. All liver biopsies obtained between date of transplant and diagnosis of PTLD was assessed for evidence of acute cellular rejection as defined by BANFF criteria. Using date of PTLD diagnosis: charts were reviewed for symptoms and clinical presentation prior to diagnosis. Radiological images: tissue pathology and clinical notes were studied to define location of PTLD and extent of disease. Tissue biopsy was evaluated for EBV using in situ hybridization for EBV encoded RNA and blood test EBV PCR quantitative measure were also obtained.

The University of Florida LT center has a protocol for EBV and PTLD care. Patients undergo routine PCR quantitative blood screening for EBV within the first two years of transplant: and if positive: further assessment for PTLD is performed. Biopsy confirms diagnosis. Once diagnosed: all patients undergo Immuno Suppression Reduction (ISR) unless clinically deemed contraindicated. Chemotherapy with Rituximab or R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Oncovin, and Prednisone) is individualized based on disease extent and clinical scenario. The actual management of involved cases in this study including medication changes and chemotherapy treatment were collected and compared to the protocol.

Patient follow up and chemotherapy response were also assessed. Complete response was noted if consequent imaging scans showed disappearance of tumor and lack of new lesions. The follow up till death or date of manuscript was recorded for each patient. Kaplan-Meier curve was used to plot overall and post-PTLD survival.

Results

Over 600 LT were performed at the University of Florida during the review period. Of those: a total of 19 adults had a biopsy confirmed

Table 2: Clinical scenario and location of PTLD diagnosis.

Sno	Time of Diagnosis†	Clinical scenario	Location	Stage	Type	EBV status‡
1	1.53	Abdominal Pain, scan showed enlarged LN	Right inguinal LN, multiple lung LN	III A	DLBCL	-
2	9.65	Several months of vague abdominal pain, scan showed multiple masses	Omental and colon	IVA	DLBCL	-
3	5.08	Headache and vertigo, scan showed multiple enhancing lesions in posterior fossa and supra-tentorial	Intracranial Supratentorial and posterior fossa masses	IIA	DLBCL	+
4	11.14	Left neck mass, scan showed activity of bilateral oropharyngeal lymphoid tissue	Left neck LN	IIA	DLBCL	-
5	12.65	Left axillary mass, scan confirmed lymphadenopathy	3.5 cm left solitary axillary LN	IA	DLBCL	-
6	0.27	Complicated hospital course following LT with ascites and pleural effusions. scan evaluations showed diffuse lymphadenopathy	Bilateral axillary, mediastinal and perihepatic LN	IVA	DLBCL	+
7	7.56	Profuse diarrhea underwent sigmoidoscopy with two masses noted	Sigmoid	IA	DLBCL	-
8	4.39	Vague abdominal pain, nausea, bloating and pruritis	Liver	IVA	DLBCL	-
9	5.86	Fever, WBC 14000, liver enzymes elevated, scan showed multiple extra lymphatic masses	Multiple retroperitoneal masses	IVB	DLBCL	-
10	2.81	Abdominal pain, nausea, early satiety and abdominal mass. scan showed multiple large soft tissue masses	Multiple Omental LN	IVB	DLBCL	-
11	11.68	Vague abdominal pain and nausea, scan showed periportal LN	Peripancreatic head and periportal LN	IIA	DLBCL	-
12	5.15	Double vision and ear pain, scan showed intracranial mass	Intracranial right petrous apex, mastoid and trigeminal cistern	IVA	DLBCL	+
13	14.31	Abdominal pain, fatigue and weight loss	Intra-abdominal cecal mass	IIB	DLBCL	-
14	6.48	Fever, chills, weight loss, abdominal pain	Liver	IVB	DLBCL	-
15	0.05	Gastritis noted on endoscopy for biliary stent removal, biopsy confirmed	gastric lymphoma	IA	MALT B-cell	-
16	22	Left side hip pain, scan showed destructive iliac lesion	Left iliac wing	IA	DLBCL	-
17	16.8	Persistent pancytopenia underwent evaluation by bone marrow biopsy, which found PTLD, scan otherwise did not show masses	Bone marrow	IA	Lymphoblastic B cell	-
18	16.4	Asymptomatic, underwent screening colonoscopy, found polyp, scan found LN involvement above and below diaphragm	Colon, left palatine LN, left cervical LN, left inguinal LN, central mesenteric LN	IIIA	DLBCL	-
19	6.25	Acute left lower abdominal pain, scan showed evidence of free air in abdomen, underwent surgery and biopsy confirmed diagnosis	Ileum	IA	DLBCL	-

† Time of diagnosis is in years from date of transplant

‡ + denotes presence of EBV in biopsied tissue, - denotes absence of EBV in biopsied tissue and lack of viremia

DLBCL: Diffuse Large B Cell Lymphoma; EBV: Epstein Barr Virus; LT: Liver Transplant; LN: Lymph Node; MALT: Mucosa associated lymphoid tissue

diagnosis of PTLD. The most common liver disease etiology as the main indication for LT was Primary Sclerosing Cholangitis (PSC). The median age at diagnosis was 50 years: with a slight male predominance at 52.6% and a majority of Caucasians (84.2%). All patients with PTLD were EBV seropositive (100%) and most were CMV seropositive (73.7%) at transplant. All patients received standard immunosuppression regimen that includes a steroid taper after LT along with a maintenance regimen that combines a Calcineurin Inhibitor (CNI) with mycophenolate for patients with an autoimmune basis for their liver diseases. Table 1 summarizes patient characteristics at time of LT.

The median time from LT to PTLD diagnosis was 6.48 years (range 0.05-22). Early PTLD: within the first year of LT: occurred in two patients (patients #6 and #15). Vague abdominal pain was a common symptom that leads to the diagnosis of PTLD. While only two patients presented with liver predominant PTLD: most patients had an extra-hepatic mass focus in the abdomen at diagnosis. In about half the patients: diagnosis occurred at a late cancer stage:

Ann Arbor Stages III or IV. The tumor pathology was diffuse large B cell lymphoma in 89.5% of the cases. All patients: except patient #12 were CD20 positive. Despite EBV seropositivity at transplant: only three patients had EBV detected in their tumor biopsy with only #3 and #6 showing viremia. Only patient #3 had CMV viremia at PTLD diagnosis. Table 2 details the circumstances of PTLD diagnosis.

Almost all patients underwent ISR as part of treatment of PTLD: except patients #6 and #9. Chemotherapy was standard in management of PTLD: most commonly by R-CHOP. Patient #15 did not receive chemotherapy due to remission using H pylori treatment and radiotherapy. Patient #17 underwent active surveillance ISR without chemotherapy.

Two patients (#7 and #14) developed recurrence of ESLD post PTLD diagnosis: due to cholestatic injury and chronic rejection respectively. Median follow up of patients from LT was 12.4 years. The median follow up from diagnosis of PTLD was 2.05 years. Of these patients: five (26.3%) passed away by date of manuscript. Cause of death was either progressive PTLD despite treatment or

Table 3: PTLD Management, Outcomes and Survival.

Sno	Management	Outcomes	Mortality and cause of Death
1	ISR + Rituximab	Despite initial improvement in PTLD burden, HCV cirrhosis recurred, and Rituximab stopped. About four years later he presented with aggressive lymphoma in spine and brain	Yes, Progressive PTLD
2	ISR + R-CHOP	Achieved CR with six cycles of R-CHOP	No
3	ISR + Ganciclovir +Rituximab	Despite treatment of intracranial lesion, subsequent evaluation two months after Dx showed 3cm lesion in left lung lobe	Yes, progressive PTLD
4	ISR + R-CHOP + XRT	Achieved CR with four cycles of R-CHOP and XRT	No
5	ISR + R-CHOP + XRT	Achieved CR with three cycles of R-CHOP and XRT	No
6	R-CHOP	PTLD progressed due to medical inability to tolerate chemotherapy	Yes, Progressive PTLD
7	ISR + Rituxan followed by R-CHOP	Achieved CR with four cycles of Rituxan followed by four cycles of R-CHOP	No
8	ISR + R-CHOP + MTX	Achieved CR with one cycle of R-CHOP and MTX	No
9	R-CHOP	Achieved CR with six cycles of R-CHOP	No
10	ISR + R-CHOP + resection	Achieved CR with six cycles of R-CHOP	No
11	ISR + chemotherapy	Achieved improvement in PTLD burden after four cycles of bendamustine-rituximab followed by one cycle R-CHOP then one cycle of R-CVP	Yes, ESLD
12	ISR + R-CHOP + MTX +XRT	Achieved CR with one cycle Intra thecal MTX and XRT for cranial involvement, and five cycles of R-CHOP	No
13	ISR + R-CHOP	Underwent three cycles of R-CHOP, lost to follow up for three months after Dx when he passed away	Yes, Unknown
14	ISR + Rituxan then R-CHOP	Achieved CR with four cycles of Rituxan followed by six cycles R-CHOP	No
15	ISR + XRT	Achieved CR with empirical treatment for H pylori followed by XRT	No
16	ISR + R-CHOP	Currently undergoing chemotherapy to date of manuscript, patient has evidence of symptomatic improvement	No
17	ISR	Patient underwent active surveillance with ISR	No
18	ISR + R-CHOP	Underwent six cycles of R-CHOP. Repeat scans	No
19	ISR + R-CHOP	Achieved CR by ISR followed by one cycle Rituxan, followed by 6 cycles of R-CHOP	No

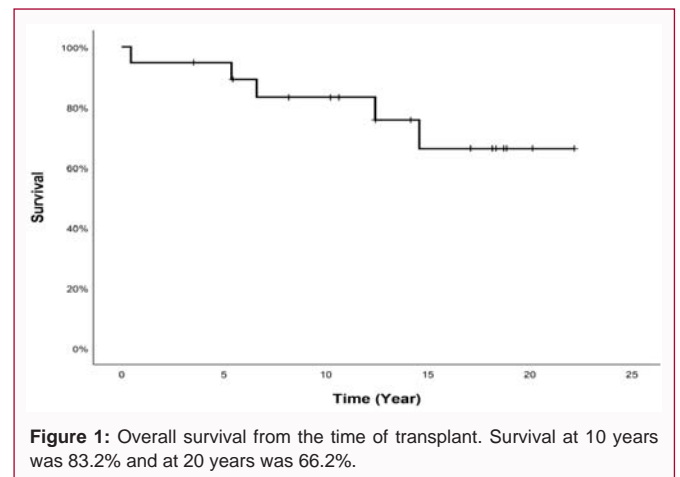
CR: Complete Remission; EBV: Epstein Barr Virus; ESLD: End Stage liver Disease; HCV: Hepatitis C Virus; ISR: Immunosuppression Reduction; LT: Liver Transplant; MTX: Methotrexate; PTLD: Post-Transplant Lymphoproliferative Disorder; R-CHOP: (Rituximab, Cyclophosphamide, Doxorubicin, Oncovin, Prednisone); R-CVP: (Rituximab, Cyclophosphamide, Vincristine, Prednisolone); XRT: Radiation Therapy

End Stage Liver Disease (ESLD). One patient received three rounds of chemotherapy and passed away within three months of PTLD diagnosis at an outside facility. Median time from LT to death was 6.6 years and from PTLD diagnosis to death was 0.3 years (3.7 months) in these five patients. The overall survival from time of LT was 83.2% at 10-years and 66.2% at 20-years. The survival from time of PTLD diagnosis was 77.6% at 5-years and 62.1% at 10-years. The specific management: outcomes and Kaplan Meier survival of these patients are noted in Table 3: Figure1,2.

Discussion

In adult LT recipients: PTLD continues to pose a clinical dilemma. Absence of standardized screening protocols and the nonspecific symptoms of disease onset make early diagnosis and treatment challenging. In this study: we identify several patterns that indicate patients at higher risk for PTLD. We found PSC as a predominant etiology in LT recipients developing PTLD. We did not detect an association between EBV status and diagnosis of PTLD. In addition: the majority of PTLD occurred late (greater than a year) and presented at an advanced stage with extra-hepatic disease. Lastly: a high mortality was noted within the first few months of diagnosis despite aggressive treatment.

Attempts of correlating the indication of LT to PTLD diagnosis has been made in prior reports but have not been conclusive. The high prevalence in PSC we noted is in line with large registries of LT showing a predominance of primary autoimmune liver disease [11,16,17]. A recent review of the US Scientific Registry of Transplant Recipients (SRTR) showed a higher rate of *de novo* cancers in PSC



patients [18]. Although other reports cite HBV: HCV and alcohol as risks for PTLD: it is worth noting the smaller sample size in these studies [12,19-21]. An important factor to consider as a risk factor is that duration and use of combinations of immunosuppressive therapy used in patients. Biopsy proven acute cellular rejection is managed by intensifying immunosuppressive therapy. In this population we noted about 58% having at least one episode of rejection. In addition: although our center utilizes standard trough target tacrolimus levels of 4-6 ng/ml: it is probable that patients with autoimmune disease are placed on higher medication dosage and longer duration to prevent recurrence of autoimmune disease and are thus more immunosuppressed predisposing to lymph proliferation [17,22].

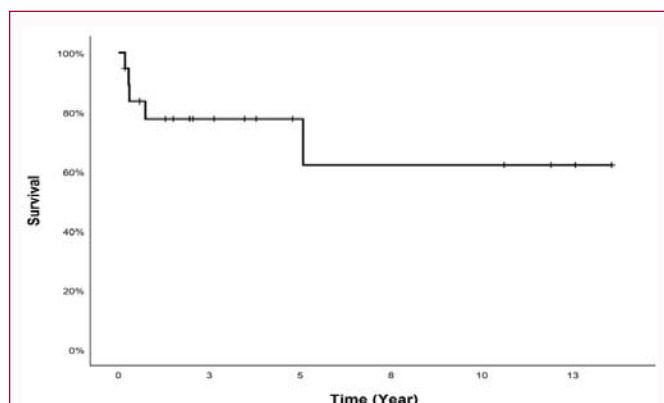


Figure 2: Overall Survival from time of PTLD diagnosis. Survival at 5 years was 77.6% and at 10 years was 62.1%.

Even with high rates of EBV seropositivity in adult population: EBV naïve patients still account for a significant percent of transplant candidates and are at increased risk of PTLD [2,8]. This risk becomes less noteworthy in liver transplant patients developing PTLD. Dharnidharka et al. [8] and Opelz et al. [23] have not shown correlation between PTLD and EBV serostatus among LT patients [8,23]. Our findings support these prior observations as none of our patients were seronegative at transplant. In addition: only a minority of our patients had EBV detected in blood or tissue pathology at time of diagnosis: suggesting sources other than EBV reactivation can attribute to PTLD. Moreover: 89.5% of our patients developed late PTLD (>1 year from transplant); and 89.5% had PTLD origin outside the donor liver: which is consistent with other studies reporting EBV negative tumors tendency to present later and outside transplanted graft [24,25].

Immunosuppression reduction is used in most of our PTLD patients along with chemotherapy. This approach is in line with our institutional protocol and recommendations from National Comprehensive Cancer Network [26]. With this management: we note a promising 5-year survival rate of 77.6% and more than 60% survival at 10-years. Several recent studies have shown similar 5 years survival post PTLD: approximately 60% at 5-years [27,28]. These favorable findings: which are contrasted to earlier reports of poor outcome: likely suggest improvement in our management of PTLD [29,30].

Despite improvement in 5-years survival: early mortality after initial diagnosis remains high. Prognostication factors have been proposed including PTLD origin: time of presentation: and EBV status. In our population: primary PTLD site does not seem to affect this grim prognosis as only two had donor liver PTLD: neither of whom died. Previous reports are also inconclusive [25,31]. In those who had extra hepatic PTLD: four passed away within one year of diagnosis: of which two were EBV negative late PLTD and though it has been suggested late PTLD can have drastically worse prognosis: this has not been shown in LT population [24,32].

In the post PTLD survival: we noted that two patient (10.5%) developed end stage liver disease requiring re transplantation: neither of whom had recurrence of PTLD but one of which was due to chronic rejection. A few studies in the pediatric population have noted greater than 30% rates of graft loss post PTLD treatment in relation to rejection [33,34]. To our knowledge: the effect of the immunosuppression modification on the donor liver survival in adult

LT is not well defined.

Some of the limitations of our analysis are its retrospective design and the single center nature. These limitations are common with rare diseases and are difficult to overcome. However: the rarity of PTLD occurrence highlights the need for these communications and multicenter collaboration to better understand this condition. In conclusion: the low incidence of PTLD in LT worldwide: along with heterogeneity in underlying etiology: presenting symptoms: location and relationship with immunosuppressive regimens: makes early diagnosis difficult. While we routinely screen for EBV: findings of EBV negative disease bring into question the need for a screening protocol beyond peripheral blood EBV measurement. For the time being: it would serve well to maintain a high suspicion of PTLD in those with PSC or autoimmune diseases and have a low threshold to test for PTLD in EBV negative patients with vague: unexplainable systemic symptoms.

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